REMARKS

I. Support for Amendments

A. Claim Amendments

Claim 16 has been amended to recite, *inter alia*, that the sense strand and the antisense strand of the siRNA molecule comprises about 14 to about 24 nucleotides that are 100% complementary to each other (*see*, specification at, *inter alia,* page 17, lines 9-22; page 17, line 27 – page 18, line 14), and about 50 to 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified (*see*, specification at, *inter alia,* page 6, lines 25-26; page 7, lines 9-26; page 11, lines 6-21). The remainder of the amendments to claim 16 are made to rephrase, clarify the language, or to provide antecedent basis and do not constitute new matter.

The amendments to the claims are made without prejudice, and Applicants expressly reserve the right to pursue the subject matter of the amended claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

II. Preliminary Matters

A. Withdrawn Rejections

Applicants thank the Examiner for reconsideration and withdrawal of the objections to the claims and certain rejections of the claims. In particular, Applicants understand that the prior rejections under 35 U.S.C. § 102(e) and the non-statutory provisional obviousness-type double patenting rejection have been withdrawn.

B. Priority

The Office asserts that U.S. Appl. Ser. No. 09/103,636 (the '636 application) fails to provide adequate support for the subject matter claimed in the instant application. In particular, the Office argues that the recitation in the claims of the term "perfect complementarity" between

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each strand of the claimed double stranded nucleic acid molecule is not found in the '636 application. Applicants have elected to amend the claim in order to remove the term "perfect complementarity" and insert the term "100% complementary" therefor, as supported in the '636 application, for example, at page 11, ln.28-30. This amendment is merely believed to resolve the priority issue asserted by the Office and it not an admission or comment concerning any alleged prior art references.

III. Claim Rejections under 35 U.S.C. § 103

Claims 16-24 stand rejected under 35 USC § 103(a) for allegedly being obvious over the combination of Fire, *et al.* and Zamore, *et al.*, in view of McCall, *et al.*, and Matulic-Adamic, *et al.* In particular, the Office asserts that Fire teaches targeting and inhibition of a target gene using an siRNA molecule between 12-30 nucleobases in length, which comprises sequence sharing 100% homology with the complement of the target gene, and full complementary between the strands. Zamore is argued to teach that optimal size range for siRNA targeting mRNA in vitro is 21-23 nucleobases. McCall is alleged to teach double stranded nucleic acid molecules of 14-24 nucleotides in length having 5' and/or 3' caps. Similarly, Matulic-Adamic is alleged to teach double stranded nucleic acid molecules of 14-24 nucleotides in length having 5' and/or 3' cap structures. The Office argues that it would have been obvious to one of ordinary skill in the art to incorporate the 5' and/or 3' cap structures, 2'-modified nucleotides, phosphorothioate linkages, and perfect complementarity into the siRNA molecules of Fire and Zamore. Applicants respectfully disagree with the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

The cited references, alone or in combination fail to teach or suggest all the elements of the claimed invention, namely a chemically modified double stranded short interfering ribonucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein:

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(a) each strand is about 14 to about 24 nucleotides in length, wherein the antisense strand comprises about 14 to about 24 nucleotides that are_complementary to nucleotide sequence of a target RNA or a portion thereof; (b) the sense and the antisense strand are 100% complementary to each other; (c) either the sense or antisense strand comprise a 5'-cap, a 3'-cap, or both a 5' and 3'-cap; and (d) about 50 to 100 percent of the nucleotides of the sense strand, the antisense strand or both comprise a chemical modification wherein the chemical modification is 2'-fluoro, 2'-*O*-methyl, 2'-H or a combination thereof.

The Office seems to apply an "obvious to try" rationale in support of its obviousness rejection. This is not the standard for a rejection based on 35 U.S.C. § 103, particularly where "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of may possible choices is likely to be successful...." (M.P.E.P. § 2145(X.)(B.)). While the disclosures of Fire and Zamore generally discuss targeting siRNAs of various sizes and RNAi mechanisms, the Office acknowledges that these references fail to teach or suggest a siRNA molecule comprising the cap structure(s), 2'-modifications (including 2'-fluoro, 2'-O-methyl), and phosphorothioate linkages. The Office relies on the disclosures of Matulic-Adamic and McCall to cure that deficiency; however, these references fail to teach or suggest targeting any RNA sequence using double stranded siRNA molecules because each disclosure relates to a different nucleic acid technology (e.g., ribozymes). Although ribozymes and siRNA are both nucleic acid-based technologies, they differ substantially both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. The modifications taught by Matulic-Adamic and McCall relate primarily to single stranded nucleic acid constructs and do not provide any insight or guidance as to particular chemical modifications that could be incorporated into any double stranded siRNAs, including those of Fire or Zamore, that would still allow for a functional molecule. As discussed above, and conceded by the Office, Fire and Zamore are also silent regarding any teaching or suggestion to the incorporation of chemically modified nucleotides in a double stranded siRNA molecule.

Applicants' position is strengthened by later publications that discuss chemically modified siRNA molecules and how the introduction of many chemical modifications can impair or extinguish siRNA activity, (*see, e.g.,* Tuschl *et al.* US Pat. Publ. 2004/0259247, paragraphs [0178] to [0179], and Elbashir *et al., EMBO Journal*, 2001, pg. 6885, left col.)). Therefore, because the Office has failed to cite any art addressing the introduction of chemical modifications that can be tolerated in siRNA molecules, and later publications in the siRNA art expressly teach that extensive modifications can obliterate siRNA activity, it could not have been obvious to make the highly modified constructs now being claimed. Thus, the present claims cannot be obvious over the cited art.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims based on 35 U.S.C. § 103(a) over Fire and Zamore, in light of Matulic-Adamic and McCall.

IV. Conclusion

Applicants respectfully request reconsideration of the pending claims and rejections in light of the above amendment and argument. If the Examiner believes a personal or telephonic conference would help expedite prosecution of the application, she is invited to contact the undersigned.

Respectfully submitted,
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